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# Implementation of HIV-Related Clinical Research in the International Setting

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## Introduction

The last twenty years have witnessed a dramatic increase in human immunodeficiency virus (HIV)-related therapeutic research conducted in international settings. Moving from a model of leadership based in a US or European institution, international sites have developed increasing autonomy and many now have the capacity for the conduct of high quality clinical research. In tandem with the increased availability of antiretroviral therapy and laboratory monitoring, investigators from resource-limited settings (RLS) now set their own research agenda, one which is relevant for their local and regional priorities.

The development of this research capacity and expertise has included many challenges ranging from overarching ethical issues, to the practicalities of maintaining continuous electrical power. Many RLS are in areas of very high disease burden and overwhelming need for clinical care and laboratory services, which compete with the resources needed for clinical trials. International aid agencies have appropriately focused on building clinical capacity for prevention and treatment services, rather than research capacity. Inadequate health care infrastructure, understaffing, and complex regulatory hurdles also contribute to the difficulties.

The editors of this supplement have had the privilege of participating in the process of development of international sites for the NIH-funded therapeutic trials networks. For example, the AIDS Clinical Trials Group (ACTG) now has 27 international clinical research sites. Developed under the leadership of Dr Constance Benson, the network has developed and implemented multiple pivotal clinical trials performed almost exclusively at the international sites, that have changed both clinical practice and management guidelines[1]. These include A5175 which evaluated alternative first line antiretroviral treatment regimens;[2] A5199 which described the neurocognitive and neurologic complications of HIV and its therapies in RLS.[3] The International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), in collaboration with the ACTG, conducted A5207 and A5208 which evaluated alternative ART regimens for the prevention of mother-to-child transmission and the consequences of single dose nevirapine therapy.[4,5] Also performed in

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RLS, the SAPIT and CAMELIA studies demonstrated the benefits of early antiretroviral therapy (ART) in patients with TB, a finding which was confirmed in A5221 and contributed to changes in treatment paradigms[6,7,8]. The most recent groundbreaking study was the HIV Prevention Trials Network (HPTN) 052/A5245 demonstrating dramatic reduction in HIV transmission by ART in discordant couples.[9] The primary paper was voted the "Science Breakthrough of the Year".[10] This trial also informs on ongoing debate about when to start antiretroviral therapy, by showing that early ART delayed the time to development of HIV-related clinical events, a finding originally shown by the CIPRA Haiti trial. [11,12]

An important component of the success of the development of the international research capacity and agenda has been community engagement and capacity development.[13–15] Community participation has been a key component of National Institute of Allergy and Infectious Diseases (NIAID) research activities since early in the HIV/AIDS epidemic, and continues to be so with the expansion of the research into RLS.[16] Community representatives are integrated at every level, from creation of the scientific agenda and priorities to approval of a concept proposal and subsequent development and implementation of a protocol.

We have developed strong collaborative relationships with many of the talented and hardworking site investigators and staff working in extraordinary conditions, and we have also had the opportunity to observe many of the issues encountered with research in the international RLS. Agenda setting, collaborating with multiple funding partners, negotiating an appropriate and achievable standard of care, and regulatory challenges including supporting nascent Institutional Review Boards (IRB) and other topics associated with multinational research made for extremely interesting discussions that we felt might also be of interest to a wider audience.

This supplement describes some of the key issues encountered in the conduct of clinical research in resource-limited settings, with authors from representative international sites. We are very grateful for funding support from the Therapeutics Research Program at the Division of AIDS.

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